agreed to reconsider the application.

It was noted that the examiner of the identical parent case, Dr. Paul Tran, *stated that the invention was free of the art of record.* While the art of record in the parent did not include patents '675 or '097 relied on by Examiner Tung, the record did contain virtually identical references. For example, reference "D8" (Brenner, "Molecular Tagging System," PCT/US95/12791), which includes the entire disclosure and claims of '097, was before Examiner Tran. And, reference "#D6" (Sibson, "Sequencing of Nucleic Acids," PCT/GB95/00109), which discloses an adaptor-based sequencing method extremely similar to that disclosed in '675, was also before Examiner Tran. Finally, it was noted that Examiner Tran was the examiner for '675, thus was intimately familiar with the technology, and was in a position to judge its relation to the present invention.

Applicant agreed to submit a description of the present invention which highlights its relationship to, and differences from, the inventions of '675 and '097, and to re-submit responses to the outstanding rejections in the case.

The Invention

The present invention is best seen as an improvement of the invention disclosed in U.S. patent '675: The crux of the invention is the use of the so-called "encoded adaptors" in a sequencing process that otherwise is very similar to that disclosed in '675[1], e.g. as defined in claim 1 of '675. Encoded adaptors are double stranded DNAs essentially the same as the "probes" of '675, except that they include an oligonucleotide tag, related to those disclosed for sorting in U.S. patent '097[2].

The diagram attached as Exhibit A illustrates how the tags of '097 are used for sequencing. The illustrated embodiment roughly corresponds to claim 21 of '097. The

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[1] The present invention is broader than that of claim 1 of '675 because it includes embodiments that do not require the step of "repeating," as illustrated in Figures 1A-1E.

[2] The preferred tags of the present invention are similar to, but not identical to, the tags of '097. The tags of '097 are so-called "combinatorial" tags because they are synthesized using a combinatorial approach in order to generate large numbers of tags, e.g. on the order of 10^8, or more. Such large numbers are required for sorting, but they are not required for identification, which typically require only a few tens or hundreds of tags. Consequently, preferred tags in the present invention are "non-combinatorial," in that they synthesized individually. Non-combinatorial tags are also preferred for identification because one has greater control over the tag sequences synthesized. This distinction is described on page 14, lines 7-18, of the specification.

crucial role of the tags of '097 occurs in step 2, where identical polynucleotides are sorted onto individual microparticles. The role of the tags of the present invention occurs in step 4, where the ends of the sorted polynucleotides are sequenced. These respective roles are also illustrated in Figure 1C of the application, where polynucleotides are shown with tags for sorting at one end (small t's), and tags for sequence identification at the opposite end (large T_{24} and large T_5).

The function of tags in the present invention is illustrated in the diagram attached as Exhibit B, which is a simplification of Figures 1A-1E of the application. The illustrated embodiment roughly corresponds to claim 1 of the present application. Target polynucleotides are cleaved with a restriction endonuclease so that they all end with the same protruding strand ("gact" in the illustration). A mixture of encoded adaptors is combined with the target polynucleotides so that only those having perfectly matched ends are ligated (i.e. those with "ctga" overhangs). The rest are washed away. The ligated encoded adaptors are then identified, i.e. the sequence "ctga" is identified, by specifically hybridizing the appropriate labeled tag complement to the tag carried by the adaptor.

Obviousness-Type Double Patenting Rejections

In the final Office Action dated 14 October 1998, the rejection of claims 1, 2, 6-8, and 11-12 under the doctrine of obviousness-type double patenting was maintained with respect to various claims of U.S. patent 5,599,675 ('675). The Examiner reiterated the argument that encoded adaptors would be obvious over the probes of '675 because of the similarity in their respective structures and functions.

Applicants respectfully disagree. First, the encoded adaptors of the present invention have a very different structure than the probes of '675 because encoded adaptors include an oligonucleotide tag, whereas the probes of '675 do not include an oligonucleotide tag. Second, the encoded adaptors function the same as the probes of '675 *only as to their common elements*, such as the protruding strand that ligates to the end of a target polynucleotide, or the type IIs restriction endonuclease recognition site which permits repeated cycles of ligation and analysis. As to identification of the ligated probe or adaptor, the encoded adaptors function quite differently from the probes of '675: The encoded adaptors are identified by specifically hybridizing a labeled tag complement to its tag, whereas a probe of '675 is identified directly by a label it carries, e.g. a fluorescent label, or the like, as described in col. 11, line 51, to col. 12, line 24, of the patent, and illustrated in Figures 1a, 1e, and 2 of the patent.

attaching a label to a known probe ↓ does not make structure novel

Finally, the is nothing in '675 to suggest to, or motivate, one skilled in the art to make the improvement disclosed in the present invention. In particular, there is no suggestion or hint as to the problem that led Applicants to the present invention, described on page 2, lines 10-21,

Not overcome any problems, etc
No unexpected results

of the specification. The Examiner inappropriately concludes obviousness based on an incorrect evaluation of the structure and function of the encoded adaptors of the invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In the final Office Action dated 14 October 1998, the rejection of claims 15-18 under the doctrine of obviousness-type double patenting was maintained with respect to claims 1-3, 11-12, 21, 25, and 27 of U.S. patent 5,604,097 ('097) when considered in view of U.S. patent 5,599,675 ('675). The Examiner merely listed the component elements of the present invention for '675 and '097 and inappropriately concluded without any basis that one of ordinary skill in the art would have combined the techniques of '675 and '097 "to increase the sensitivity of nucleic acid sequence determination."

Applicants respectfully disagree and submit that the Examiner is inappropriately basing the rejection on a "hindsight" analysis of the invention. Accordingly, Applicants request that the rejection be withdrawn.

Rejections Based on 35 U.S.C. 103

In the final Office Action dated 14 October 1998, the rejection of claims 1-10, 12-14, and 19-23 under 35 U.S.C. 103(a) as being unpatentable over Brenner, U.S. patent 5,599,675 ('675) was maintained. The Examiner re-iterated arguments made in the first Office Action; namely, that "one having ordinary skill in the art would have been motivated to use an encoded adaptor in the method of Brenner to determine a nucleic acid sequence because it would have been expected to serve the same purpose as the probe of Brenner."

Applicants respectfully disagree. The Examiner's entire analysis of the invention is based only on similarities to the invention described in '675, and completely ignores significant differences. Applicants submit that the Examiner has failed to establish a prima facie case of obviousness because significant differences have not been shown to be mere design choices or otherwise routine modifications of the basic invention of '675. In particular, there is no finding of a specific suggestion in '675 that would lead one skilled in the art i) to recognize or appreciate the technical problem addressed by encoded adaptors, ii) to determine that such a problem could be solved by combining oligonucleotide tags with adaptors, or iii) to recognize any other reason for combining oligonucleotide tags and adaptors. Without such a finding the Examiner has merely identified the components of Applicants' invention in the cited references, and *by hindsight* has deemed it obvious to combine them. Applicants respectfully request that the rejection be withdrawn.

Not evidence to contrary

In the final Office Action dated 14 October 1998, the rejection of claims 11 and 15-16 under 35 U.S.C. 103(a) as being unpatentable over Brenner ('675) in view of Brenner ('097) was maintained.

Applicants respectfully continue to disagree with the rejection for the reasons set forth in their prior response. Namely, the Examiner has merely identified the elements of the invention in the cited references, but has not provided any reasoning based on the disclosures for why one with ordinary skill in the art would be led to combine the elements to arrive at Applicants' invention. Moreover, Applicants disagree that the excerpt of '097 in column 5, lines 51-56 discloses "the formation of the Hoogsteen triplex *for identifying nucleic acid sequence* (emphasis added), as stated on page 8, lines 2-3, of the Office Action. The except reads as follows:

> In reference to a triplex, the term ["perfectly matched"] means that the triplex consists of a perfectly matched duplex and a third strand in which every nucleotide undergoes Hoogsteen or reverse Hoogsteen association with a basepair of the perfectly matched duplex.

Clearly, this excerpt is a definition of the term "perfectly matched" as it related to triplexes. It has nothing to do with how triplexes might be used. In particular, it states nothing about identifying nucleic acid sequences with triplexes. Accordingly, Applicants submit that the rejection has no grounds and should be withdrawn.

In the final Office Action dated 14 October 1998, the rejection of claims 17-18 under 35 U.S.C. 103(a) as being unpatentable over Brenner ('675) in view of Brenner ('097) was maintained.

Applicants respectfully continue to disagree with the rejection for the reasons set forth in their prior response. Namely, the Examiner has merely identified the elements of the invention in the cited references, but has not provided any reasoning based on the disclosures for why one with ordinary skill in the art would be led to combine the elements to arrive at Applicants' invention. Applicants submit that the Examiner is merely using hindsight to reconstruct Applicants' invention from elements that are purportedly disclosed in the cited references. Accordingly, the rejection should be withdrawn.

In the final Office Action dated 14 October 1998, the rejection of claims 24-29 under 35 U.S.C. 103(a) as being unpatentable over Brenner '097 was maintained.

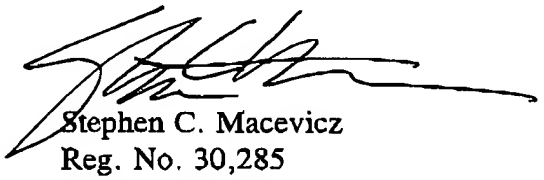
Applicants respectfully continue to disagree. '097 nowhere teaches or suggests the use of oligonucleotide tags in combination with an adaptor. '097 only directly teaches the making and using of oligonucleotide tags to *sort* polynucleotides onto solid phase supports (making tags: col.

6, line 33, to col. 9, line 21; and using tags: col. 9, line 24, to col. 16, line 52; and the examples). In every case, oligonucleotide tags are attached to polynucleotides of unknown sequence and are used to specifically hybridize the resulting conjugates to tag complements attached to a solid phase support. In the instant invention, an oligonucleotide tag forms a part of an encoded adaptor and is used to specifically hybridize a labeled tag complement in order to identify the nucleotides in the protruding strand of the encoded adaptor. Thus, the function of the tags and tag complements is quite different and, therefore, one with ordinary skill in the art would not be led to use oligonucleotide tags of '097 as labeling means. Accordingly, Applicants respectfully request that the rejection be withdrawn.

In view of the above, Applicants submit that the claims as written fully satisfy the requirements of Title 35 of the U.S. Code, and respectfully request that the rejections thereunder be withdrawn and the claims be allowed.

If any additional time extensions are required, such time extensions are hereby requested. If any additional fees not submitted with this response are required, please take such fees from deposit account **12-2491**.

Respectfully submitted,



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